CLAIMS

1. A method of detecting a disease or a disease susceptibility trait in an organism, wherein said disease or said disease susceptibility trait is associated with a mutation or mutations in a subject gene, comprising:

(a) isolating a biological sample from said organism;

(b) immunologically quantitating the amount of wild-type protein expressed by said subject gene in said sample, and the amount of a reference protein expressed by a second gene in said sample;

(c) calculating the ratio of the amount of the wild-type protein expressed by said subject gene in said sample to the amount of the reference protein expressed by said second gene in said sample;

(d) determining whether or not any wild-type protein expressed by said subject gene is present in said sample, or whether or not said calculated ratio reflects an abnormally low level of said wild-type protein expressed by said subject gene in said sample; and

(e) concluding that if no wild-type protein is present in said sample, that said subject gene contains a mutation in each of its alleles, or, that if the ratio calculated in step (c) indicates that there is an abnormally low level of wild-type protein in said sample, that said subject gene contains a mutation in one of its alleles, and that if either is the case, that the subject organism is affected by the disease or the disease susceptibility trait associated with said mutation or mutations.

2. The method of Claim 1 wherein step (d) comprises comparing the ratio calculated in step (c) to a mean of ratios of amounts of said wild-type protein expressed from said subject gene to amounts of said reference protein in comparable biological samples from organisms of the same taxonomic classification as the subject organism, that are unaffected by said disease or by said disease susceptibility trait.

3. The method of Claim 1 wherein said organism is a vertebrate.

4. The method of Claim 3 wherein said vertebrate is a mammal.

5. The method of Claim 4 wherein said mammal is a human.

6. The method of Claim 4 wherein said reference protein is actin, tubulin, or glyceraldehyde-3-phosphate dehydrogenase.

7. The method of Claim 1 wherein said mutation is or said mutations are selected from the group consisting of germline mutations and somatic mutations.

8. The method of Claim 7 wherein said mutation is a germline mutation, or wherein said mutations are germline mutations.

Sub A2

9. The method according to Claim 1 wherein said biological sample is selected from the group consisting of body fluids, tissue specimens, tissue extracts, cells, cell lysates, cell extracts, supernatants from normal cell lysates, supernatants from preneoplastic cell lysates, and supernatants from neoplastic cell lysates.

10. The method according to Claim 9 wherein said body fluids are selected from the group consisting of blood, serum, plasma, semen, breast exudate, gastric secretions, fecal suspensions, bile, saliva, tears, sputum, mucous, urine, lymph, cytosols, ascites, pleural effusions, amniotic fluid, bladder washes, bronchoalveolar lavages, and cerebrospinal fluid.

Sub A3

11. The method according to Claim 9 wherein the cells are peripheral blood lymphocytes; the cell lysates are lysates of peripheral blood lymphocytes; the cell extracts are from peripheral blood lymphocytes; and the lysates of normal, preneoplastic or neoplastic supernatants are from peripheral blood lymphocytes.

12. The method of Claim 1 wherein said biological sample is selected from the group consisting of tissue samples, tissue extracts, normal cells, lysates of normal cells, and supernatants from lysates of normal cells.

13. The method of Claim 1 wherein said method is diagnostic, or diagnostic/prognostic for cancer, or for susceptibility to cancer.

14. The method of Claim 1 wherein said mutation is or said mutations are selected from the group consisting of truncating-causing mutations and mutations that cause allelic loss.

15. The method of Claim 14 wherein said mutation is or said mutations are selected from the group consisting of nonsense mutations, frameshift mutations, promoter mutations, enhancer mutations, splice site mutations, null mutations, and poly-A tail mutations.

16. The method of Claim 1 wherein the subject gene is selected from the group consisting of ATM, APC, BRCA1, BRCA2, CFTR, c-myb, dystrophin, E-cadherin, EMD, FAA, IDS, MLH1, MSH2, MSH6, NF1, NF2, p16, PKD1, PKD2, PMS1, PMS2, PTCH, TGFBR2, and VHL genes.

17. The method according to Claim 1 wherein said disease is, or said susceptibility trait is for a disease selected from the group consisting of ataxia-telangiectasia, hemangioblastoma, renal cell carcinoma, pheochromocytoma, colon cancer, colorectal cancer, gastrointestinal cancer, breast cancer, ovarian cancer, endometrial cancer, prostate cancer, pancreatic cancer, biliary tract cancer, cystic fibrosis, hematologic malignancies, Duchenne muscular dystrophy, genitourinary cancers, gynecologic cancers, Emery-Dreifuss muscular dystrophy, Fanconi anemia, Hunter syndrome, neurofibromatosis type 1, neurofibromatosis type 2, familial melanoma, polycystic kidney disease, nevoid basal carcinoma, and von Hippel-Lindau disease.

18. The method of Claim 1 wherein said subject gene is the APC gene, and said disease is or said disease susceptibility trait is for familial adenomatous polyposis.

19. The method of Claim 1 wherein the subject gene is a mismatch repair gene.

20. The method of Claim 19 wherein the subject gene is selected from the group consisting of the MLH1, MSH2, MSH6, PMS1, and PMS2 genes; and said disease is or said disease susceptibility trait is for hereditary non-polyposis colon cancer.

21. The method of Claim 20 wherein the subject gene is either the MLH1 gene or the MSH2 gene.

22. The method of Claim 1 wherein the amounts of said wild-type protein expressed by said subject gene, and of said reference protein are determined by Western blot analysis, by immunoprecipitation and then by Western blot analysis, by flow cytometry, by EIA, by ELISA, by RIA, by competition immunoassay, by dual antibody sandwich assay, by chemiluminescent assay, by bioluminescent assay, by fluorescent assay, or by agglutination assay.

23. The method of Claim 1 which is automated.

24. A method of detecting a disease or a disease susceptibility trait in an organism, wherein said disease or said disease susceptibility trait is associated with a mutation or mutations in one of two or more subject genes, comprising:

(a) isolating a biological sample from said organism;

(b) immunologically quantitating the amount of wild-type protein in said sample, that is expressed by each of the subject genes;

(c) calculating the ratio of the amount of the wild-type protein expressed by one of said subject genes in said sample, to the amount of wild-type protein expressed by the other subject gene in said sample, or to each of the amounts of wild-type protein expressed by each of the other subject genes in said sample;

(d) determining whether a wild-type protein expressed by either of the subject genes, or by any of the subject genes is absent from said sample, or whether the

ratio or ratios calculated in step (c) reflects or reflect an abnormally low level of a wild-type protein expressed by either of the subject genes, or by any of the subject genes in said sample; and

(e) concluding that if a wild-type protein known to be normally expressed by one of the subject genes is not present in said sample, that that subject gene contains a mutation in each of its alleles, or that if the ratio or ratios calculated in step (c) indicates or indicate that there is an abnormally low level of a wild-type protein expressed by one of the subject genes in said sample, concluding that that subject gene contains a mutation in one of its alleles; and, in either case, determining that the subject organism is affected by the disease or the disease susceptibility trait associated with said mutation or mutations.

25. The method of Claim 24 wherein step (d) comprises comparing the ratio or ratios calculated in step (c) to the comparable mean or means of ratios calculated from the amounts of wild-type proteins expressed by the subject genes in comparable biological samples from organisms of the same taxonomic classification as the subject organism, that are unaffected by said disease or by said disease susceptibility trait.

26. The method of Claim 24 wherein said organism is a vertebrate.

27. The method of Claim 26 wherein said vertebrate is a mammal.

28. The method of Claim 27 wherein said mammal is a human.

29. The method of Claim 24 wherein said mutation is or said mutations are selected from the group consisting of germline mutations and somatic mutations.

30. The method of Claim 24 wherein said mutation is a germline mutation, or wherein said mutations are germline mutations.

31. The method of Claim 24 wherein said mutation is or wherein said mutations are selected from the group consisting of truncating-causing mutations and mutations that cause allelic loss.

32. The method of Claim 31 wherein said mutation is or said mutations are selected from the group consisting of nonsense mutations, frameshift mutations, promoter mutations, enhancer mutations, splice site mutations, null mutations, and poly-A tail mutations.

33. The method of Claim 24 wherein said biological sample is selected from the group consisting of body fluids, tissue specimens, tissue extracts, cells, cell lysates, cell extracts, supernatants from normal cell lysates, supernatants from preneoplastic cell lysates, and supernatants from neoplastic cell lysates.

34. The method of Claim 33 wherein said body fluids are selected from the group consisting of blood, serum, plasma, semen, breast exudate, gastric secretions, fecal suspensions, bile, saliva, tears, sputum, mucous, urine, lymph, cytosols, ascites, pleural effusions, amniotic fluid, bladder washes, bronchoalveolar lavages, and cerebrospinal fluid.

35. The method of Claim 33 wherein the cells are peripheral blood lymphocytes; the cell lysates are lysates of peripheral blood lymphocytes; the cell extracts are from peripheral blood lymphocytes; and the lysates of normal, preneoplastic or neoplastic supernatants are from peripheral blood lymphocytes.

36. The method of Claim 24 wherein said biological sample is selected from the group consisting of tissue samples, tissue extracts, normal cells, lysates of normal cells, and supernatants from lysates of normal cells.

37. The method of Claim 24 wherein said method is diagnostic or diagnostic/prognostic for cancer or for susceptibility to cancer.

38. The method of Claim 24 wherein the subject genes are selected from the group consisting of ATM, APC, BRCA1, BRCA2, CFTR, c-myb, dystrophin, E-cadherin, EMD, FAA, IDS, MLH1, MSH2, MSH6, NF1, NF2, p16, PKD1, PKD2, PMS1, PMS2, PTCH, TGFBR2, and VHL genes.

39. The method of Claim 24 wherein said disease is, or said susceptibility trait is for a disease selected from the group consisting of ataxia-telangiectasia, hemangioblastoma, renal cell carcinoma, pheochromocytoma, colon cancer, colorectal cancer, gastrointestinal cancer, breast cancer, ovarian cancer, endometrial cancer, prostate cancer, pancreatic cancer, biliary tract cancer, cystic fibrosis, hematologic malignancies, Duchenne muscular dystrophy, genitourinary cancers, gynecologic cancers, Emery-Dreifuss muscular dystrophy, Fanconi anemia, Hunter syndrome, neurofibromatosis type 1, neurofibromatosis type 2, familial melanoma, polycystic kidney disease, nevoid basal carcinoma, and von Hippel-Lindau disease.

40. The method of Claim 24 wherein the subject genes are mismatch repair genes.

41. The method of Claim 40 wherein the subject genes are selected from the group consisting of the MLH1, MSH2, MSH6, PMS1, and PMS2 genes; and said disease is or said disease susceptibility trait is for hereditary non-polyposis colon cancer.

42. The method of Claim 41 wherein the subject genes are the MLH1 gene and the MSH2 gene.

43. The method of Claim 24 wherein the amount of each wild-type protein expressed from each subject gene is determined by Western blot analysis, by immunoprecipitation and then by Western blot analysis, by flow cytometry, by EIA, by ELISA, by RIA, by competition immunoassay, by dual antibody sandwich assay, by

chemiluminescent assay, by bioluminescent assay, by fluorescent assay, or by agglutination assay.

44. The method of Claim 24 which is automated.

45. A method of detecting a disease or a disease susceptibility trait in an organism, wherein said disease or said disease susceptibility trait is associated with a mutation or mutations in a subject gene, comprising:

(a) isolating a sample of normal cells from said organism;

(b) immunologically quantitating the amount of wild-type protein expressed by the subject gene in said sample;

(c) determining whether any wild-type protein is present in said sample, and if so, whether the amount of wild-type protein present in said sample is abnormally low in comparison to the amount of wild-type protein expressed by the subject gene in a control sample; and

(d) if said wild-type protein is not present in said sample, concluding that the subject gene has a mutation in each of its alleles; or if the amount of said wild-type protein in said sample is determined to be abnormally low in comparison to the amount of wild-type protein in the control sample, concluding that the subject gene has a mutation in one allele; and in either case, correlating the conclusion with the subject organism having the disease or the disease susceptibility trait associated with said mutation or said mutations.

46. The method of Claim 45 wherein said organism is a vertebrate.

47. The method of Claim 46 wherein said normal cells are peripheral blood lymphocytes.

48. The method of Claim 45 wherein the amount of wild-type protein in said sample is determined to be about 50% of the amount of wild-type protein in the control sample, and concluding that the subject gene has a mutation in one allele.